REMARKS

In view of these comments, applicants respectfully request reconsideration of the present application.

I. Interview Summary

Undersigned counsel for applicants wishes to thank Examiner Shaw and her supervisor, Examiner Kapushoc, for extending the courtesy of a personal interview conducted on December 8, 2010. During the interview of the pending action was discussed with respect to the cited reference, Waki and Okamoto.

II. Rejections Withdrawn

Applicants gratefully acknowledge the examiner's withdrawal of objections to the abstract and of Section 103 rejections based on Wong/Okamoto and Wong/Okamoto/Waki.

III. Obviousness Rejection Over Waki in View of Okamoto

Claims 1-3, 5, 8, and 9 remain rejected over the combination of Waki *et al.*, *Am. J. Pathology* 161: 399-403 (2002), with Okamoto *et al.*, *Proc. Nat'l Acad. Sci. USA* 94: 5367-71 (1997). The Office admits that "Waki does not teach a method of quantitatively determining the frequency of epimutation of a particular gene in said population of cells" (action, page 5). The Office also acknowledges that "Waki does not teach a method wherein the normal tissue is normal peripheral blood" (*id.*).

Thus, the Office looks to Okamoto to cure these significant deficiencies of the primary reference. As detailed below, however, the posited Waki/Okamoto combination not only fails to substantiate the alleged *prima facie* case, since Waki teaches away from the claimed invention, but also is itself improper under section 103, since the skilled artisan never would have generalized to the present context the salient teachings of Okamoto, which relate to a parent of origin-specific gene. Withdrawal of this remaining rejection is warranted, therefore.

A. Waki Does Not Suggest But Rather Teaches Away from the Claimed Invention

A "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2143.03(VI). Thus, the fact that a reference teaches away from a feature recited in the claims means that the cited prior art is unavailable to rationalize an obviousness rejection.

Looking to Waki, particularly his Table 1, and taking notice of the hMLH1 methylation status indicated there, one of ordinary skill would have gleaned that, for a variety of tumors, there is no methylation in a diversity of organs. In direct contravention of this impression from Waki, applicants' present teachings indicate that one should find methylation of MLH1 in a diversity of organs from individuals who have had cancers in which MLH1 was methylated. For instance, see the specification at pages 10-14 (Example 1) and pages 14 and 15 (Example 2).

Accordingly, Waki teaches that, to assess the early development of cancer, one should assay for the presence of an epimutation in the tissue in which disease is developing or will develop. By the same token, Waki would have led the skilled artisan away from an expectation that the risk of developing disease could be assessed, as in the claimed invention, by searching for methylation in organs that had not developed and would not develop a cancer (see also subsection C, *infra*). Waki thus actually teaches away from applicants' claimed invention.

More specifically, Waki's Table 1 shows no epimutation for hMLH1, and yet the patient later developed cancer. Absent hindsight informed by applicants' invention, therefore, the skilled artisan could not have intuited how or even whether to predict risk of cancer from the results shown in Table 1. To the contrary, Waki's samples that were taken from tumor tissue -- Table 1 focuses on hMLH1 methylation status in brain, liver, rectal, lung, pancreatic, ovarian lymphoma, lung, and colon tissue -- did not exhibit methylation.

Again, these observations would have led the skilled artisan away from the claimed invention. Exacerbating this teaching-away impact of Waki, vis-à-vis the person of ordinary skill, is the fact that Waki also lacks the sort of negative control that, in principle, might have prompted the skilled artisan to pursue an approach akin to applicants'. That is, Waki omits any case where epimutation was lacking and the patient did not develop cancer. Waki also shows no case where there was epimutation in a healthy individual who later developed cancer.

B. Okamoto Cannot be Combined Waki as a Matter of Fact and Law

"While obviousness does not require absolute predictability, *at least some degree of predictability is required*." MPEP § 2143.02(II) (emphasis added). It is apparent from the foregoing, however, that no plausible combination of the Waki reference with any secondary reference(s) of record could evidence the *a priori* predictability in the art that is the touchstone of a sustainable section 103 rejection. *See also* MPEP § 2141(I), citing *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) (obviousness of combining allegedly known elements turns on "whether the [resultant] improvement is more than the predictable use of [the] elements according to their established functions").

This lack of predictability is all the more compelling for the asserted combination of Okamoto, which concerns a parent of origin-specific gene, with Waki, which does not. Nevertheless, the Office argues that, "[s]ince both Waki and Okamoto are drawn to methods concerning detecting methylation they are considered to be compatible," *i.e.*, reasonably combinable references.

Applicants respectfully submit that this argument is erroneous as a matter of both fact and law, however.

In the first instance, applicants have emphasized that the claimed invention explicitly excludes parent of origin-specific genes. This is so because, although imprinted genes normally are subject to epigenetic silencing (see discussion below), a "tumor suppressor gene" as presently recited ***never*** is normally subject to epigenetic silencing. Loss of imprinting is an aberration of a normal process of epigenetic silencing, while silencing of a tumor suppressor is always abnormal.

Faced with these points heretofore, however, the Office has demurred on the ground that Okamoto is invoked only "to teach quantitatively determining the frequency of epimutation of a particular gene in said population of cells and method wherein the normal tissue is normal peripheral blood." It is true that both Waki and Okamoto address epimutation phenomena. Yet, the Office has taken Okamoto completely out of proper context, a factual error that has obscured a fundamental distinction between the epimutation phenomenon addressed in Okamoto, which affected a parent of origin-specific gene, and that epimutation that was Waki's focus, which affected a gene that is <u>not</u> parent of origin-specific.

So informed, one of ordinary skill in the art would have readily appreciated that Waki cannot be combined with Okamoto in the manner posited by the examiner here.

That is, the skilled artisan would have known that some 100 to 200 human genes are expressed only from the paternal or the maternal allele. This peculiar expression pattern is the result of genomic imprinting, an epigenetic process by which the male and the female germ line confer a parent of origin-specific mark or "imprint" on certain chromosomal regions. See, *e.g.*, Morison *et al.*, *Hum. Mol. Genet.* 7: 1599-609 (1998) (copy appended). The persistence of such parent of origin-specific gene silencing, which causes reduced or absent expression of a specific allele of a gene in somatic cells of the offspring, is understood to reflect an evolutionary pressure, possibly related to a conflict between the parental genomes over nutritional demands. For instance, see Monk *et al.*, *Hum. Mol. Genet.* 18: 3066-74 (2009), and Constancia *et al.*, *Nature* 417: 945-48 (2002) (copies appended). Imprinting is thus a feature of all mammalian genomes, influencing genes that regulate cell growth, behavior, signaling, cell cycle, and transport.

Although *loss* of imprinting can be a cause of disease, as in the case of many Wilms tumors in children, see Ravenel *et al.*, *J. Nat'l Cancer Inst.* 93: 1698-703 (2001) (copy appended), the skilled artisan would have understood that the mere *incidence* or frequency of this epimutation phenomenon, as considered in Okamoto, bears no relation to disease etiology. By the same token, the skilled artisan would not have expected or have been motivated to correlate a disease risk with the frequency of this type of epimutation.

In order to establish a case for obviousness based on multiple references, the Office must identify a reason, implicated in the prior art, that would have prompted the person of ordinary skill to combine the elements allegedly drawn from that art. As the U.S. Supreme Court stated *KSR*, cited above, the Office must look to (i) interrelated teachings of the cited reference, (ii) the effects of demands known to the design community or present in the marketplace, and (iii) the background knowledge possessed by a person having ordinary skill in the art, all to the ends of determining whether there was an apparent reason to combine the known element in the fashion claimed by the patent at issue.

Against this background of governing precedent, the Office has combined (1) Waki, directed to non-neoplastic gastric epithelia (**not a parent of origin-specific gene**), and (2) Okamoto, directed to Wilms tumor (**a parent of origin-specific gene**). None of the *KSR* considerations (i) – (iii), *supra*, could have justified this "apples-versus-oranges" conflation of teachings. Parent of origin-specific genes, which are excluded from the present claims, are subject to genomic imprinting whereby, as discussed above, gene expression is dependent on the sex of the parent whence the gene was inherited. This parental bias would have confounded any notion by the skilled artisan to gauge cancer risk by reference to the methylation status of a parent of origin-specific gene.

For the same reasons, the posited combination of Waki and Okamoto would not have occurred to the skilled artisan. Pursuant to *KSR* and MPEP § 2143.01 (VI), therefore, the combination of Waki with Okamoto is impermissible as a matter of law under section 103, which also justifies a withdrawal of the remaining obviousness rejection.

C. No Principled Combination of Waki and Okamoto Could Have Presaged Applicants' Claimed Approach to Assessing Cancer Risk by Reference to "Normal Tissue" in a "Healthy Individual"

Overarching the Office's stated position regarding obviousness in this regard is a mistaken view that applicants' claimed approach entails seeking out an indication that disease will develop or is developing by looking for an epimutation in the tissue where the disease will occur. To the contrary, however, the claimed invention is keyed to detecting epimutation in tissues where disease will never occur, not on searching for epimutation in the tissue where disease is expected to arise.

This focus, so at odds with the teachings of the cited art, is reflected in the present recitations of "a healthy individual" and "normal tissue" (claim 1) and of "normal peripheral blood …," etc. (claim 2). It is well-illustrated, too, in applicants' example of MLH1, which shows that the risk of developing colorectal and other cancers can be assessed by looking, for instance, at peripheral blood leukocytes of healthy individuals, including persons who have never had cancer and those who, if and when cancer develops, will not suffer a blood cancer.

Applicants' claims and underlying specification thus highlight the notion of "determining the frequency of eipimutation," as presently recited, at a site distal to that where cancer may

develop. Nowhere is this notion even hinted at by the prior art represented by Waki or Okamoto. It necessarily follows, therefore, that no principled combination of Waki and Okamoto could have led one of skill in the art to assessing cancer risk by reference to "normal tissue" in a "healthy individual," vindicating the patentability of the claimed invention.

CONCLUSIONS

In view of the foregoing, applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Shaw is invited to contact the undersigned directly, should she feel that any issue warrants further consideration.

Respectfully submitted,

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